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Possible Mutagenic Properties and Carcinogenic Action of the Irritant Gaseous Pollutants NO_2, O_3, and SO_2

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Carcinogenic or cocarcinogenic effects of NO_2, O_3, and SO_2 have not been proven to date with sufficient reliability. However, nitrosamine formation after exposure to NO_2- or O_3- induced decrease in benzpyrene hydroxylase are potential hazards. A final revaluation of a possible cocarcinogenic action of SO_2 requires further experimental studies.

Epidemiological studies would be of the greatest value in assessing the possibility of mutagenic properties and carcinogenic action of the irritant gaseous pollutants NO_2, O_3, and SO_2. To date, there has been only one such study (*1*), an investigation of the frequency of lung cancer in Los Angeles, where oxidant levels are high, as compared to the frequency in the San Francisco/San Diego area. However, considering the multiplicity of possible parameters in carcinogenesis and the relatively short period of exposure (1958–1963) to high oxidant levels, no detailed conclusions can be drawn from this study.

Experimental studies on the carcinogenic and mutagenic effects of an agent are naturally restricted to animals. The following is a brief account of what we know today from studies on animals exposed to NO_2, O_3, and SO_2.

Ever since Druckrey and Preussmann (*2*) postulated the formation of nitrosamines in the lung by reaction of NO and NO_2 with amines, a possible indirect carcinogenic action of oxides of nitrogen has been under discussion. Using *in vitro* experiments, Sander et al. (*3*) demonstrated that interactions of nitrite and amines lead to the production of nitrosamines in the stomach. However, this reaction requires an acidic medium; nitrosamine formation in a medium of neutral pH, as in the lung, has not been proven (*4*). It has been found that nitrite is formed in the lungs upon contact with NO_x and that nitrosamines are generated in lung homogenates (*5, 6*). This evidence supports the hypothesis of Druckrey and Preussmann. The possibility of a mutagenic effect of NO_x may be suggested in the light of *in vitro* experiments showing that nitrite is a highly potent mutagen (*7–10*).

Brinkmann, Lamberts, and Veninga (*11*) first postulated radiomimetic properties of O_3 when comparing the effects of ultraviolet radiation and O_3 on human skin. This assumption has been supported by later investigators, and a review on this topic has been given by Veninga (*12*).

From the experimental results of Zelac et al. (*13, 14*) it is evident that O_3 has direct mutagenic properties. After 5 hr exposure of hamsters to 0.2 ppm O_3 (320 $\mu g/m^3$), the frequency of chromosomal breaks increased in the lymphocytes. A comparison with the effect of 230 rad x-radiation indicated that at these concentrations O_3 was the more strongly acting agent. A combined exposure to O_3 and x-radiation did not show a synergistic effect. *In vitro* experiments on chick embryos (*15*) and human cell cultures (*16*) also showed the mutagenic property of O_3; the observed chromosome aberrations were apparently dose-dependent.

Formation of malignant tumors after long-term exposure to NO_2 or O_3 has not been observed. Henschler and Ross (*17*) and Ross and Henschler (*18*) exposed mice or hamsters to high concentrations of NO_2 (40 ppm; 76 mg/m^3) for up to 16 months and did not see an increase in tumor rate. However, inflammation with cell proliferation in the terminal bronchioli—and thus a higher mitosis rate probably leading to a higher susceptibility to other carcinogens—was present in all animals.

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Stupfel et al. (*19*) did not find an increased tumor rate in long-term NO_x exposures. On the other hand, when increased NO_x levels were combined with motor vehicle exhausts, an increased tumor rate was observed.

Formation of malignant tumors has not been observed in mice after long-term exposure to O_3 at levels of 2.5 ppm (4900 $\mu g/m^3$/2 hr daily/5 weeks) (*20*) or 1 ppm (1960 $\mu g/m^3$ for 15 months) (*21*). Exposure to ambient Los Angeles air was also without effect as far as the formation of malignant tumors was concerned (*22, 23*). An increased incidence of adenoma was found in the O_3 experiments. O_3 induced a decrease in benzpyrene hydroxylase in animals exposed to 0.75–1.0 ppm (1470–1960 $\mu g/m^3$ for 3 or 1.5 hr) (*1, 24-26*) and caused delayed benzpyrene elimination (*27*).

From the experimental results of Laskin et al. (*28*) a cocarcinogenic action of SO_2 may be suggested when combined with benzo[a]pyrene. Rats were exposed to 10 mg/m^3 benzo[a]pyrene and about 10 mg/m^3 SO_2 1 hr/day, 5 days/week. After 98 weeks, two of 21 rats had developed squamous cell carcinoma. In another group exposed to 10 mg/m^3 benzo[a]pyrene and 10 mg/m^3 SO_2 for 1 hr/day with an additional exposure to 30 mg/m^3 SO_2 6 hr/day, 5 days/week, five out of 21 rats had developed squamous cell carcinoma after 98 weeks. However, from the comparison with a control group of only three animals exposed to pure air or sulfur dioxide only, no firm conclusions can be drawn.

In conclusion, although the carcinogenic or cocarcinogenic effects of NO_2 have not been proven to date, nitrosamine formation is a potential hazard. Furthermore, the effects of exposure to O_3 on the metabolic handling of benzpyrene must be kept in mind when discussing this pollutant's possible carcinogenicity. Concerning SO_2, there is only little evidence regarding a cocarcinogenic action; before a final evaluation can be made more experiments are necessary.

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